Helicobacter pylori and Risk of Gastroenteritis

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Background. Helicobacter pylori infection is thought to modify susceptibility to gastroenteritis.

Methods. Members of northern California households with an index case of gastroenteritis were interviewed regarding recent episodes and tested for H. pylori. Conditional logistic regression was used to evaluate the risk of secondary gastroenteritis within households matched for members with secondary gastroenteritis (cases) and those without symptoms (control subjects). Case and control subjects were also tested for hepatitis A virus (HAV).

Results. Of 801 households, 205 (26%) had at least 1 member with secondary gastroenteritis, of which 116 (56%) also included at least 1 member without symptoms (158 case and 285 control subjects). Compared with uninfected members and adjusting for age, those with antibodies to only 1 infection were at a decreased risk of secondary gastroenteritis (odds ratio [OR] for H. pylori infection, 0.25 [95% confidence interval [CI], 0.08–0.82]; OR for HAV, 0.45 [95% CI, 0.23–0.87]). Having antibodies to both H. pylori and HAV did not add to this negative effect (adjusted OR, 0.39 [95% CI, 0.18–0.84]).

Conclusions. H. pylori did not increase the risk of gastroenteritis in these households. A strong negative association between H. pylori infection and gastroenteritis is likely explained by prior exposure and immunity to other enteric pathogens.

Helicobacter pylori, which is now recognized as an etiologic factor in peptic ulcer disease [1] as well as gastric carcinoma [2, 3], infects ~80% of individuals in developing countries but is rapidly disappearing with economic development [4]. Because the acute phase of infection may be associated with transient hypochlorhydria, it has been speculated that infection may increase susceptibility to enteric pathogens. Sullivan et al. [5] reported an increased risk of chronic diarrhea, compared with healthy control subjects, among infected age-matched Gambian children with malnutrition. In a nested case-control design, Clemens et al. [6] found an increased risk of severe cholera among H. pylori–infected subjects without vibriocidal antibodies. Similarly, in an urban slum, H. pylori infection was twice as common among subjects with typhoid fever (Salmonella typhi) [7] than in neighborhood control subjects. Passaro et al. [8] reported increased diarrhea episodes among Peruvian infants with recent H. pylori seroconversion.

Not all studies have consistently revealed a link, however. In a Thai orphanage, Isenbarger et al. [9] found no association between seroconversion and diarrheal disease. Some investigators have even speculated that local inflammatory factors induced by infection may be protective [10]. In a cross-sectional study of elementary school–age children in Germany, Rothenbacher et al. [11] reported that infection was associated with a reduced frequency of diarrheal illnesses.

Physiologic arguments are of little help in resolving discrepancies in epidemiological findings, because H. pylori could be argued to increase or decrease susceptibility to enteric pathogens. Depending on the age at acquisition and the anatomical site of colonization, for example, H. pylori decreases gastric acid secretion in some people—thereby potentially reducing the effectiveness of the gastric-acid barrier to intestinal pathogens—but increases gastric-acid secretion in others [12].

Understanding the role of H. pylori is difficult because of the many confounding factors that may influence results. Socioeconomic status, ethnicity, crowding, household sanitation, and prior infection with enteric pathogens are all potentially associated both with H. pylori and with gastroenteritis. To address these issues,
we designed a prospective study to evaluate the incidence of gastroenteritis in a community-based cohort of US households at high risk of *H. pylori* infection. To minimize confounding, our analysis compared *H. pylori*'s effects within households, rather than among individuals from different households. Moreover, we simultaneously evaluated the effect of another marker for infection—hepatitis A virus (HAV)—in gastroenteritis. We now report the association of secondary gastroenteritis with *H. pylori* infection within this large, predominately Hispanic cohort in the San Francisco Bay Area.

**SUBJECTS, MATERIALS, AND METHODS**

**Study Design and Population**

The Stanford Infection and Familial Transmission study is a prospective cohort design that was begun in 1999 to evaluate the association of *H. pylori* infection with gastroenteritis. Northern California households with episodes of acute gastroenteritis were recruited by community outreach, as well as through cooperating community health-care settings. The health-care groups included 7 general medicine outpatient clinics, 2 emergency rooms, and 3 pediatric clinics in Santa Clara and San Mateo counties. All but 1 of the health-care settings were public health systems serving low-income families. Households with gastroenteritis were also recruited through the 2 county environmental health surveillance programs. Informed consent was obtained from all subjects, or their guardians, in accordance with guidelines for the conduct of clinical research of Stanford University and the US Department of Health and Human Services.

Health-care providers within each health-care setting were asked to identify patients (index cases) who presented with diarrhea and/or vomiting that was of suspected infectious etiology. The provider then asked the patient or guardian whether they would be willing to be contacted by study personnel. If the patient agreed, a brief telephone interview elicited eligibility criteria for the study. Through June of 2003, there have been 3344 household referrals, of which 76% have come from public health-care providers. Eligible households needed to include at least 2 consenting household members, including an index case with diarrhea and/or vomiting lasting ≤14 days without a known noninfectious explanation, such as pregnancy, chemical poisoning, or drug or treatment adverse effect. Of these 3344 referrals, 1003 households (30.0%) were eligible and enrolled (figure 1). If eligible, a household visit was scheduled within 12 days of the onset of illness in the index case. At this household visit, written consent was obtained from all participating household members. Those household members who consented to participate were administered a structured questionnaire regarding risk factors for *H. pylori* infection and the onset, frequency, and duration of gastroenteritis symptoms. Serum samples were obtained for the determination of *H. pylori* infection. Households were given a calendar and asked to record all subsequent episodes of diarrhea or vomiting within the household. Three months later, a second visit was arranged to obtain follow-up information about episodes of diarrhea and vomiting and to repeat specimen collection. All visits were conducted by research staff with phlebotomy certification who were fluent in the preferred language of the household.

**Laboratory Methods**

*H. pylori* infection was diagnosed using an ELISA for IgG described elsewhere [13]. This assay is 91% sensitive and 98% specific for infection in adults. Using 33 serum samples obtained from children who had endoscopic confirmation of infection (15 positive and 18 negative; courtesy of P. Sherman, Department of Paediatrics and Microbiology, Hospital for Sick Children, University of Toronto, Ontario, Canada), we established the sensitivity and specificity of the assay for children <16 years of age. A positive value was adjusted to 75% of the adult standard; this 75% cutoff was 86% sensitive and 100% specific in these children. Subsequent assessment of these cutoff points in 50 adults and children with breath test–confirmed *H. pylori* indicated 100% sensitivity and specificity. Serum samples were stored at −80°C after testing.

In the present analysis, only laboratory results from the first household visit were used. Indeterminate results (~4% of runs) were considered to have negative results. Because we were concerned that serum ELISA testing is not accurate in children <2 years of age, these children were not included in the analysis of the role of *H. pylori* in secondary gastroenteritis.

**HAV.** Stored serum samples from 158 persons with secondary gastroenteritis and 285 persons in the same households who reported no symptoms (see Statistical Analysis) were tested using the Medionost HAV EIA for the detection of antibodies (IgG) against HAV. When the Boehringer-Mannheim enzyme test is used as a reference, this HAV IgG EIA has a sensitivity and specificity of 94.1% and 99.25%, respectively [14]. Results were interpreted qualitatively, according to the manufacturer’s instructions. Initial runs were conducted in duplicate, to establish reliability. Because of limited quantities, second-visit serum samples were substituted for first-visit samples in the case of 10 persons.

**Analytic Methods: Definitions**

**Primary gastroenteritis.** A primary case of acute gastroenteritis was defined as the first case, within a household, of loose or watery stool occurring ≥5 times/day in a child <2 years old or ≥3 times/day in a person ≥2 years old or at least 1 instance of vomiting in a person of any age. A case of gastroenteritis was considered to be coprimary if the onset began <48 h after onset in the first case within the household.

**Secondary gastroenteritis.** To distinguish secondary gastroenteritis from illness occurring from the same point source
as that in the index case, a secondary case was defined as a case of diarrhea or vomiting beginning ≥2 days after the beginning and ≤5 days after the end of an episode in another household member. A second episode occurring in a primary case did not constitute secondary transmission. An example of the derivation of secondary gastroenteritis case status is shown in figure 2.

**Individual episode.** An episode of gastroenteritis began with the first day of diarrhea or vomiting and ended on the day before 96 h without diarrhea or vomiting occurred.

**Household episode.** A household episode was defined as a period extending from the first date of acute illness in the household to the end of the last episode with at least 96 h in a row without symptoms for all household members. A household was considered to have completed follow-up for an episode when ≥5 days had elapsed from the end of the most recent individual episode in the household.

**Child.** A child was defined as a person <18 years old.

**Eligible.** An eligible subject was ≥2 years old, provided that sufficient serum was available for *H. pylori* testing, and, if selected for the matched analysis, also HAV testing, and provided that responses to interviews sufficient to classify symptoms as primary, secondary, or absent were available. To be eligible for analysis, a household had ≥2 members who met these criteria.

**Statistical Analysis**

Bivariate comparisons using categorical variables were tested by $\chi^2$ test and with continuous variables by Students’ $t$ test or, when parametric assumptions were not appropriate, the Wilcoxon test. The primary analysis used conditional logistic regression to evaluate the odds of *H. pylori* infection among household contacts who had secondary gastroenteritis (cases) and contacts within the same household who reported no symptoms during a household episode (control subjects). Stratified conditional logistic regression, matching case and control subjects within a household [15], was used to evaluate the risk
of secondary gastroenteritis in association with H. pylori infection and to adjust for other person-level characteristics. The outcome for the analysis was secondary gastroenteritis (yes vs. no, with cases of primary gastroenteritis excluded). In addition to serological evidence of H. pylori infection, other person-level characteristics examined in the household model included age (2–17 or ≥18 years), sex, and sharing a bed. We also modeled the association of H. pylori and secondary gastroenteritis in 738 households with outcomes of interest, using unconditional logistic regression. The dependent variable for this analysis was secondary gastroenteritis status (yes vs. no, excluding primary cases). A generalized estimating equation [15] was used to account for within-household variation with an exchangeable correlation matrix.

RESULTS

Between January 2000 and June 2003, a total of 1003 households (5731 individuals) met eligibility criteria and were enrolled. Of these, 335 (33%) had completed a household episode of gastroenteritis at the time of the first visit; of those 668 households that required a second visit to complete the household episode, 466 (70%) were successfully visited and 202 (30%) were lost to follow-up. The most common reason for loss to follow-up was relocation. Thus, a total of 4514 individuals in 801 households (80% of eligible households) provided information on gastroenteritis. Among the 4514 individuals, 2513 (56%) were ≥2 years old, were present at the home visit, and consented to participate. These 2513 subjects in 801 households made up the substrate for our analysis.

Household characteristics. Of the 801 households, 78% were referred by public health providers (table 1). More than 70% reported Spanish to be the primary language of the household, and, in 81% of 639 households that reported country of origin, at least 1 member had been born in Latin America (median, 3 members). The median household size was 5 member (range, 2–20 members), including a median of 2 children and 3 adults; the mean number of household members per bedroom was 2.5 (range, 0.4–8 members/bedroom). Of 75% households reporting, 56% reported an annual household income <$30,000. The median educational level, defined by the household member with the greatest number of years of formal education, was 12 years. Households without complete follow-up information were of somewhat greater size (median, 6 vs. 5 members; P = .02), had fewer enrolled members (median, 67%; P = .04), were of lower income (68% with annual household income <$30,000; P = .02), and were more likely to have
been referred by a public health provider (85% vs. 77%; \( P = .02 \)). They were similar with respect to primary language (75% vs. 70% Spanish-speaking; \( P = .13 \)), median educational level (12 years; \( P = .75 \)), and the mean number of persons/bedroom (2.5 persons/bedroom; \( P = .08 \)).

**Gastroenteritis.** The 801 households reported a median 4 days of symptomatic enteric illness (range, 1–33 days), involving 1–8 household members, or, on average, ∼46% of participating members and 31% of known household members. Of the 4514 household members, 947 (21%) were considered to be primary or coprimary cases, 298 (6.6%) to be secondary cases, 3066 (68%) reported no symptoms, and 203 (4.5%) reported symptoms without dates and therefore could not be classified as to primary or secondary onset. A total of 86% of households (686) had only 1 primary case, and 14% (115) had \( >1 \) primary case (range, 2–6 cases). The 298 secondary cases occurred in 205 households (26%), including 144 (70%) with 1 secondary case and 61 (30%) in which 2–5 were classified as secondary cases.

Of 2513 participating members, 2447 subjects \( \geq 2 \) years old had serum results available. Of these, samples from 38.25% tested positive for \( H. pylori \), including from 18.0% of 885 subjects who were 2–17 years old and from 49.7% of 1562 subjects \( \geq 18 \) years old. At least 1 infected household member (range, 1–9 members) was identified in 67% (536/801) of households, including 232 households (29%) in which \( \geq 2 \) participants \( \geq 2 \) years of age were infected.

**Conditional logistic regression.** To minimize confounding, our primary analysis used conditional logistic regression to identify the risk factors for secondary gastroenteritis within households. As a consequence, only the subset of households with discordant outcomes (at least 1 member with secondary gastroenteritis and 1 asymptomatic member; \( n = 116 \)) contributed information to the conditional logistic regression model. Of 205 households with at least 1 member with a secondary case, 28 had no asymptomatic members, and 61 did not have at least 1 case patient and 1 control subject \( \geq 2 \) years old with serum results available. Compared with 685 other households (table 1, column 2), this subset of households was more likely to have been referred by a public health provider (87% vs. 75%; \( P = .01 \)), be of larger size (median, 7 vs. 5 members; \( P = .01 \)), and include more children 2–17 years old (median, 2 vs. 1 children; \( P = .01 \)) but were similar to other households in educational level, income, ethnicity, number of primary or coprimary case patients, and sleeping density. A greater percentage of household members \( \geq 2 \) years old were likely to participate in the study (median, 100%; \( P < .01 \)).

These 116 households had a total of 765 members, of whom 448 provided outcomes of interest—162 secondary cases and 286 with no symptoms. The remaining 317 household members had primary episodes (\( n = 134 \)), were children \( <2 \) years old (\( n = 20 \)) or older individuals without serum results (\( n = 162 \)), and 1 individual could not be classified by episode (\( n = 1 \)).

In univariate conditional logistic regression models, \( H. pylori \)-infected household members were approximately one-half as likely as uninfected household members of the same household to have secondary gastroenteritis (odds ratio [OR], 0.48 [95% confidence interval [CI], 0.30–0.76]; \( P < .01 \)). Adults (age \( \geq 18 \) years) were also significantly less likely to have secondary cases (OR, 0.45, [95% CI, 0.30–0.70]; \( P < .01 \)). Sex was not a

### Table 1. Characteristics of 801 households.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All households (( n = 801 ))</th>
<th>Matched households(^a) (( n = 116 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total members, no.</td>
<td>4514</td>
<td>765</td>
</tr>
<tr>
<td>Members living in household, median (range), no.</td>
<td>5 (2–20)</td>
<td>7 (3–20)</td>
</tr>
<tr>
<td>Referred by public health-care provider, no. (%)</td>
<td>615 (77)</td>
<td>101 (87)(^c)</td>
</tr>
<tr>
<td>Household members, median, no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 2 ) years old</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(2–17 ) years old</td>
<td>1</td>
<td>2(^b)</td>
</tr>
<tr>
<td>(\geq 18 ) years old</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Members (\geq 2 ) years old participating, median, %(^c)</td>
<td>75</td>
<td>100(^b)</td>
</tr>
<tr>
<td>Spanish as primary language, no. (%)</td>
<td>560 (70)</td>
<td>89 (76)</td>
</tr>
<tr>
<td>Households with (&gt;1 ) member born in Latin America, no. (%)(^a)</td>
<td>514 (80)</td>
<td>75 (82)</td>
</tr>
<tr>
<td>Households with income &lt;$30,000/year, no. (%)(^a)</td>
<td>339 (56)</td>
<td>54 (85)</td>
</tr>
<tr>
<td>Members with primary episodes/household, median (range), no.</td>
<td>1 (1–6)</td>
<td>1 (1–3)</td>
</tr>
<tr>
<td>Age of members with primary episodes, median (range), years</td>
<td>3.8 (0–89)</td>
<td>3.7 (0–55)</td>
</tr>
<tr>
<td>Highest household education, median, years</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^a\) Households with at least 1 member with a secondary case and at least 1 asymptomatic member with \( Helicobacter pylori \) serological test results.

\(^b\) \( P < .05 \), vs. 685 unmatched households.

\(^c\) Age \(\geq 2 \) years and available for \( H. pylori \) serological testing.

\(^d\) Percentage based on a 59% response rate.

\(^e\) Percentage based on 75% a response rate.
significant predictor of the risk of secondary gastroenteritis \((P = .39)\). There was a trend toward increased risk if the subject shared a bed with another person \((OR, 1.4 [95\% CI, 0.87–2.2]; P = .18)\). Unconditional logistic regression that used a generalized estimating equation to account for household clustering in 738 households with eligible subjects revealed similar results \((unadjusted OR for \textit{H. pylori} infection, 0.58 [95\% CI, 0.43–0.77] and 0.69 [95\% CI, 0.50–0.94], adjusting for age and for sharing a bed).

**H. pylori antibody exposure.** Within the 116 matched households, serum samples were available for HAV testing from 443 \((98.8\%)\) individuals, including 158 with secondary gastroenteritis and 285 control subjects \(4\) with secondary gastroenteritis and \(1\) without symptoms did not have serum samples remaining for HAV antibody testing). Overall, \(69\%\) of subjects tested positive for HAV, including \(25\%\) of children and \(80\%\) of adults. Most \(87.6\%\) \textit{H. pylori}–positive subjects were also infected with HAV \((table 2)\). In univariate analysis, HAV exposure was associated with a significantly lower incidence of secondary gastroenteritis \((OR, 0.39 [95\% CI, 0.24–0.65])\).

In multivariate analysis \(table 3\), adjusting for age, household members with only \textit{H. pylori} were less likely to have gastroenteritis, compared with uninfected household members \((OR, 0.25 [95\% CI, 0.08–0.82])\). Similarly, household members with only HAV antibodies were less likely to have gastroenteritis \((OR, 0.45 [95\% CI, 0.23–0.87])\). The combination of the 2 infections, however, did not appreciably augment this effect \((-0.06 for negative interaction). The presence or absence of \textit{H. pylori} infection did not materially affect the risk of gastroenteritis in people with HAV antibodies.

**DISCUSSION**

In this prospective study of predominately low-income, Hispanic households in northern California, we found that \textit{H. pylori} did not increase the risk of gastroenteritis in people \(\geq 2\) years old. In contrast, \textit{H. pylori} infection had a significant negative association with gastroenteritis. Several pieces of evidence, however, suggest that this negative effect reflects unidentified confounding rather than a true physiological effect. In particular, a negative effect was observed for HAV antibodies similar to that for \textit{H. pylori} infection. Moreover, the negative effect of \textit{H. pylori} was observed primarily in HAV antibody–negative individuals, and not in HAV antibody–positive individuals. Were \textit{H. pylori} physiologically protective, one would have expected equal negative effect in both groups. The antagonism between \textit{H. pylori} and HAV in the occurrence of gastroenteritis—that is, the negative interaction observed—is best explained by a common confounder that contributes to both the association of HAV and \textit{H. pylori} with gastroenteritis. High levels of exposure in early life to intestinal pathogens and the development of partial immunity may be one such confounder. Repeated exposures to common pathogens such as Norwalk and rotavirus, which may account for \(60\%–80\)% of cyclical infectious disease outbreaks in industrialized countries \([16]\), are known to confer at least partial or transient resistance to subsequent infection \([17–19]\). If so, a waning of this effect in adults might be expected, as we observed. Thus, \textit{H. pylori} and HAV may both mark prior exposure and immunity to other enteric pathogens that cause disease.

Yet, teleologically, it is appealing to think that \textit{H. pylori} would have a true protective effect against gastroenteritis. Such a finding could explain why \textit{H. pylori} has successfully maintained a high prevalence in developing countries—that is, it provides a survival advantage in regions where gastroenteritis remains a leading cause of childhood mortality \([20]\). Moreover, it is physiologically plausible that both \textit{H. pylori} and prior HAV infection truly protect against gastrointestinal illness. In addition to increasing gastric acid output in some individuals, \textit{H. pylori} could cause bystander effects that are hostile to the passage of intestinal pathogens. For example, gastric infection might enhance mucosal immunity, with increases in secretory IgA \([21]\), the up-regulation of inflammatory cytokines \([22]\), and B cell recruitment. Moreover, it is known that gastric enzymes may be required for the activation of some viral gastroenteritis pathogens, a process that is potentially disrupted by \textit{H. pylori} infection \([23, 24]\). HAV, on the other hand, is a member of the picornavirus family, several members of which are considered to be causes of diarrheal disease \([25, 26]\). Cross-reactive antibodies between HAV and these other picornaviruses could ostensibly create a level of protection against gastroenteritis. Picornavirus infections are considered to be a rare cause of diarrhea, however, would be unlikely to account for the relatively large negative effect observed. Moreover, the fact that the OR for samples with both \textit{H. pylori} and HAV did not differ from that of samples with HAV alone is difficult to explain by use of physiologic models. The results of a very recent study, however, indicated that HAV infection may cause the primary differentiation of CD4 cells toward the Th1 phenotype, shifting the human immune system from a Th2- to a Th1-type response \([27]\). In humans, this differentiation may result in decreased atopic disease \([28]\). \textit{H. pylori} is also known to activate a systemic Th1 response. Thus, both organisms could decrease the incidence of diarrhea by activating the gut immune response, which potentially explains why the combination of infections provides.

**Table 2. Association between \textit{Helicobacter pylori} infection and hepatitis A virus (HAV) infection.**

<table>
<thead>
<tr>
<th>\textit{H. pylori} serological test result</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>169 (38.2)</td>
<td>24 (5.4)</td>
<td>193 (43.6)</td>
</tr>
<tr>
<td>Negative</td>
<td>136 (30.7)</td>
<td>114 (25.7)</td>
<td>250 (56.4)</td>
</tr>
<tr>
<td>Total</td>
<td>305 (68.9)</td>
<td>138 (31.1)</td>
<td>443 (100)</td>
</tr>
</tbody>
</table>

**NOTE.** \(\chi^2 = 55.9, P < .001\).
no additive protection, versus infection with either organism individually.

The principal limitations of our findings include uncertainty regarding the etiology of the gastroenteritis episodes and the possibility of selection bias. Symptomatic gastroenteritis is vastly underreported, and the causative agent is rarely established. Our study design did not permit the sensitive detection of causative organisms, which could have been helpful in dissecting the physiology of our findings. Furthermore, our criteria for establishing an index case of infectious gastroenteritis, which included a single episode of vomiting of probable infectious origin, may have been liberal. However, among 116 index cases, only 1 household was included that had a single instance of vomiting lasting 1 day. The exclusion of this household did not change our results. Approximately 20% of households were lost to follow-up before complete information on household cases of gastroenteritis could be obtained. Although these households—which tended to be of lower socioeconomic status—may have had an increased likelihood of household transmission, this would not have affected our outcome strongly, because comparisons were made within, rather than between, households. More problematic is the fact that, within households, ∼75% of household members ≥2 years old were available and participated in the study. Although this number was not unexpected, we cannot exclude the possibility that self-selection within households was biased with respect to H. pylori infection and gastroenteritis. Because subjects were not informed of H. pylori test results until the second visit, knowledge of infection status is less likely to have influenced follow-up rates. Although scheduled at the family’s convenience, home visits often occurred during late afternoon, when adult females and school-age children were more likely to be available. Although symptomatic illness was likely to have been an incentive for participation, the great majority of individuals are unaware of their H. pylori infection status, and most infected people have no symptoms. Thus, we feel that it is unlikely that incomplete participation biased the association between H. pylori and outcome.

Prior studies relating H. pylori to gastroenteritis have yielded conflicting results. Some have shown an increased risk of gastroenteritis, and others have shown a negative effect [9, 11]. Studies that have examined specific agents—typhoid [7] and cholera [6, 29]—have shown increased disease with H. pylori infection. Given the spectrum of outcomes associated with H. pylori and the variable distribution of gastroenteritis pathogens worldwide, the contradictory results could all be correct. Gastric acidity in the setting of H. pylori varies by host genetics [30] and the duration of infection. In addition, not all gastroenteritis pathogens are equally sensitive to the gastric environment. For example, Vibri choler a is exquisitely sensitive to acid, whereas Shigella species can be highly resistant [31]. Depending on the distribution of pathogens within a population, the effects of H. pylori infection may differ. Unfortunately, bias and confounding can also explain the conflicting results that have been observed. Although these observational studies have adjusted for host factors, such as age and malnutrition [5], and environmental factors, such as neighborhood [7] or community [6], data from randomized clinical trials—many of which are under way to address other outcomes (i.e., to prevent cancer)—may be the only route to a definitive answer.

Gastroenteritis remains a leading killer of children in developing countries. Our findings do not support our a priori hypothesis that H. pylori increases the incidence of gastroenteritis. Rather, the data suggest that the organism could have a negative association that may be explained by prior environmental exposures and/or partial immunity to other enteric pathogens. As investigators move toward the development of new H. pylori vaccines and treatments, it is imperative to better understand this interaction, so that decisions on whom to vaccinate, where, and when, can be based on a solid understanding of likely risks and benefits.

Acknowledgments

We thank William Brown and Tyson Holmes, Division of Biostatistics, Department of Health Research and Policy, Stanford University School of

### Table 3. Risk of secondary gastroenteritis by Helicobacter pylori infection, hepatitis A virus (HAV) infection, and age (adult vs. child).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>Age adjusted OR (95% CI)</th>
<th>Fully adjusted a OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori</td>
<td>0.48 (0.30–0.76)</td>
<td>0.66 (0.39–1.12)</td>
<td></td>
</tr>
<tr>
<td>HAV uninfected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV infected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV</td>
<td>0.39 (0.24–0.65)</td>
<td>0.56 (0.31–1.01)</td>
<td>0.45 (0.23–0.87)</td>
</tr>
<tr>
<td>H. pylori uninfected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. pylori infected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>0.46 (0.30–0.70)</td>
<td>0.61 (0.35–1.05)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; OR, odds ratio (reference, concordant negative individual).

* a Includes age (adult vs. child), HAV, H. pylori, and the interaction between H. pylori and HAV (P = .05, adjusting for age).
References


30. El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 poly-